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EXAMINER	
SWOPE, SHERIDAN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,058	HARDIE ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14,19-29 and 31-35* is/are pending in the application.

4a) Of the above claim(s) *1,2,6-12,14,21-29 and 31-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5,19 and 20* is/are rejected.

7)☒ Claim(s) *3-5, 19, and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' filing of December 14, 2010, in response to the action mailed June 14, 2010, is acknowledged. It is acknowledged that Claim 16 has been cancelled and Claims 3 and 19 have been amended. Claims 1-12, 14, 19-29, 31-35 are pending. Applicants' further election, in their communication of December 21, 2010, of SEQ ID NO: 9 as the STRAD polypeptide is acknowledged. The elected invention is directed to a composition comprising an LKB1 polypeptide comprising residues 44-343 of SEQ ID NO: 6, the STRAD polypeptide of SEQ ID NO: 9 comprising a C- terminal pseudokinase domain, said C-terminal pseudokinase domain comprising the C- terminal sequence Trp-Glu-Phe, and an M025 polypeptide comprising SEQ ID NO: 11 as well as a method, using said preparation and the substrate of SEQ ID NO: 110, for identifying modulators of LKB1. Claims 1, 2, 6-12, 14, 21-29, and 31-35 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 3-5, 19, and 20 are hereby reconsidered.

Priority

Claims 3-5, 19, and 20 do not receive the benefit of any priority date because they introduce New Matter; see below. In addition, it is noted that none of PCT/GB04/03096, GB 0316725.1, or GB 0330078.7 discloses SEQ ID NO: 8. In response to this action, it is requested that Applicants point out support for all recited sequences in each priority document.

Claim Objections

Claims 3-5, 19, and 20 are provisionally objected to for reciting non-elected subject matter.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-5, 19, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

For Claims 3(a) and 19(ii)(A), the phrase "capable of binding LKB1" renders the claims indefinite. It is unclear whether said phrase means the full-length LKB1 AMPK is capable of binding or specifically residues 1-19 of SEQ ID NO: 110 of AMPK are capable of binding LKB1. The skilled artisan would not know the metes and bounds of the recited invention. Claims 4, 5, and 20, as dependent from Claim 3 or 19, are indefinite for the same reason. For purposes of examination, it is assumed that "capable of binding LKB1" means the full-length LKB1 AMPK is capable of binding LKB1.

For Claim19(ii)(C), "SEQ ID NO: 159 and SEQ ID NO: 15" is improper Markush language and should be corrected to "SEQ ID NO: 159 or SEQ ID NO: 15". ". Claim 20, as dependent from Claim 19, is indefinite for the same reason.

Claims 3-5, 19, and 20 are rendered indefinite for improper antecedent usage as follows.

For Claim 3(a), the phrase "capable of binding LKB1" should be corrected to "capable of binding the LKB1". Claims 4 and 5, as dependent from Claim 3, are indefinite for the same reason.

For Claim 3(b), the term "MO25" should be corrected to "the MO25 polypeptide". Claims 4 and 5, as dependent from Claim 3, are indefinite for the same reason.

For Claim 3(c), the term "STRAD" should be corrected to "the STRAD polypeptide". Claims 4 and 5, as dependent from Claim 3, are indefinite for the same reason.

For Claim 19(ii)(B), the term "MO25" should be corrected to "the MO25 polypeptide". Claim 20, as dependent from Claim 19, is indefinite for the same reason.

For Claim 19(ii)(C), the term "STRAD" should be corrected to "the STRAD polypeptide". Claim 20, as dependent from Claim 19, is indefinite for the same reason.

Any subsequent rejection, based on clarification of the above phrases and terms, will not be considered a new ground for rejection.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claims 3-5, 19, and 20 under 35 U.S.C. 112, first paragraph/enablement for reasons set forth in the prior action, is maintained.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. These arguments are not found to be persuasive for the reasons following each argument.

(A) The Examiner has taken the position that the specification enables an affinity purified complex comprising a recombinant LKB1 polypeptide comprising residues 44-343 of SEQ ID NO: 6, a recombinant human STRAD protein with a C-terminal Try-Glu-Phe tail, and the recombinant human MO25 of SEQ ID NO: 11.

(A) Reply: Applicants have misconstrued the statement in the prior action as to what is enabled. As stated in the prior action:

> "The specification is enabling for preparations, isolated from human HEK-293 cells and Rat-2 cells, comprising endogenous LKB1, STRAD, and MO25 polypeptides. In addition, as disclosed by the specification, the prior art provides enablement for an affinity purified complex comprising a recombinant LKB1 polypeptide comprising residues 44-343 of SEQ ID NO: 6, a recombinant human STRAD protein with a C-terminal Trp-Glu-Phe tail, and the recombinant human MO25 of SEQ ID NO: 11 (Boudeau et al, 2003[a])."

Boudeau et al, 2003a (cited in the specification) teaches purification of complexes comprising human or rat LKB1/STRADα/MO25α , wherein, more likely than not, the STRADα protein comprises a C-terminal WEF tail (Fig. 3). The prior action did not state that complexes comprising any protein, having any function of any STRAD protein and having any structure comprising a C-terminal Trp-Glu-Phe tail, are enabled.

(B) Claims 3 and 19 have been amended such that: (1) LKB1 variants are now claimed of at least 90% homology to positions 44-343 of SEQ ID NO: 6; (2) LKB1 polypeptides are now claimed that phosphorylate an AMPK comprising a sequence having at least 90% homology to residues 1-19 of SEQ ID NO: 110 in a T-loop binding domain and capable of binding to LKB1; (3) STRAD polypeptides are now claimed comprising a sequence having at least 90% homology to SEQ ID NO: 9 or 10 (in addition to the C-terminal tail of Trp-Glu- Phe); and (4) MO25 polypeptides are now claimed having at least 90% homology to one of the listed sequences.

(B) Reply: It is acknowledged that the claims have been so amended. However, the scope of said amended claims is not enabled for the following reasons.

Guo et al, 2004 teaches that the percentage of random single-substitution mutations, which inactivate a protein, using a protein 3-methyladenine DNA glycosylase as a model, is 34% and that this number is consistent with other studies in other proteins (pg 9206, parg 4). Guo et

al further show that the percentage of active mutants for multiple mutations appears to be exponentially related to this by the simple formula $(0.66)^X$ x 100% where X is the number of mutations introduced (Table 1). Applying this estimate to the LKB1 protein set forth by residues 44-343 of SEQ ID NO: 6, 90% identity allows up to 30 mutations within said protein. Thus, only $(0.66)^{30}$ x 100% or 3.8 x 10^{-4}% of random mutants having 90% identity would be active. Applying this estimate to the STRAD protein set forth by SEQ ID NO: 9, 90% identity allows up to 44 mutations within said 431 amino acid protein. Thus, only $(0.66)^{44}$ x 100% or 1.5 x 10^{-6}% of random mutants having 90% identity would be active. For the MO25 protein of SEQ ID NO: 159, only $(0.66)^{38}$ x 100% or 1.4 x 10^{-5}% of random mutants having 90% identity would be active.

The claims recite a complex of the above described genera of LKB1, STRAD, and MO25 proteins. As an example, said complex can be represented by proteins having 90% identity to 44-343 of SEQ ID NO: 6, 90% identity to SEQ ID NO: 9 (431 residues), and 90% identity to SEQ ID NO: 11 (341 residues). Applying Guo's estimate to said complex, 90% identity allows up to 108 mutations within said 1072 amino acid complex. Thus, only $(0.66)^{108}$ x 100% or 3.2 x 10^{-18}% of random mutant complexes having 90% identity to the complex of 44-343 of SEQ ID NO: 6, SEQ ID NO: 9, and SEQ ID NO: 11 would be active.

Some current techniques in the art (i.e., high throughput mutagenesis and screening techniques) would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants, despite even this being an enormous quantity of experimentation that would take a very long time to accomplish. But finding a few mutants within several million or more, as in the claims to the above complex would not be possible.

Moreover, the claims recite a complex comprising any one of two STRAD proteins and five MO25 proteins. In addition, since the claims recite an AMPK having essentially any structure comprising a peptide having at least 90% identity to residues 1-19 of SEQ ID NO: 110, the genus of encompassed AMPK polypeptides is essentially unlimited.

While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Considering the scope of the claims, sufficient guidance has **not** been provided in the instant specification.

For these reasons and those explained in the prior actions, rejection of Claims 3-5, 19, and 20 under 35 U.S.C. 112, first paragraph/enablement, is maintained.

Written Description

Rejection of Claims 3-5, 19, and 20 under 35 U.S.C. 112, first paragraph/written description, for reasons set forth in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. These arguments are not found to be persuasive for the reasons following each argument.

The specification contains an adequate number of examples of the claimed compositions such that the subject matter of the claims is sufficiently described. Example 1 describes the isolation of a LKB1/MO25/STRAD complex from a number of mammalian cell lines by immunoprecipitation ([0161]-[0242]).

(A) For example, LKB1/MO25/STRAD complex comprising both the α and β isoforms of STRAD and MO25 is described by Example 1.

HeLa cells that had been transfected with a functional LKB1 gene fused to an N- terminal FLAG epitope and were used to immunoprecipitate LKB1 from HeLa cell lysate were described ([0162]- [0164]). The transfected HeLa cells were constructed as per Boudeau et al, 2003a (enclosed); Boudeau et al. in turn used constructs as described in Saptoka et al. 2001 (enclosed) (see page 850, column 1, under "DNA Constructs" in Boudeau, which refers to reference 17. Sapkota et al. cloned functional LKB1 from mice (see page 19470, column 2, under "Cloning of Mouse LKBI"). As shown in the attached BLAST search (Exhibit A), positions 44-343 share 96% sequence homology with GenBank accession number NP_035622.1, which is LKB1 from Mus musculus. Therefore this LKB 1 falls within the scope of the claims. The transgenic LKB1 co-precipitated with STRADα and MO25α. These would have been the endogenous proteins from the host HeLa cells, so they would have been human STRADα (SEQ ID NO: 9) and human MO25α (SEQ ID NO: 11).

(A) Reply: Said example does not described the genus of all complexes comprising any protein having at least 90% identity to residues 44-343 of SEQ ID NO: 6 wherein the protein phosphorylates any polypeptide comprising a sequence with at least 90% identity to SEQ ID NO: 1-19 of SEQ ID NO: 110, plus any protein having at least 90% identity to SEQ ID NO: 9 or 10, and any protein having at least 90% identity to SEQ ID NO: 11, 13, 15, 22, or 159. For example, no proteins having (i) 90% identity to residues 44-343 of SEQ ID NO: 6 wherein the protein phosphorylates any polypeptide comprising a sequence with at least 90% identity to SEQ ID NO: 1-19 of SEQ ID NO: 110, (ii) 90% identity to SEQ ID NO: 9 or 10, or (iii) 90% identity to SEQ ID NO: 11, 13, 15, 22, or 159, or complexes thereof are described. As explained above, the genus of all said complexes is extremely large. Disclosure of a complex comprising a LKB1

protein having 96% identity with residues 44-343 of SEQ ID NO: 6, the STRADα of SEQ ID NO: 9, and the MO25α of SEQ ID NO: 11 does not described the claimed genus of complexes such that the skilled artisan would recognize Applicants were in possession of the recited invention.

(B) In paragraph [0164] an experiment is described in which endogenous LKB1 was precipitated from two lines of cells: human HEK-293 cells and Rat-2 cells (rat embryo fibroblast). As shown in Fig. 3A, in both lines of cells STRADα and MO25α co- precipitated with endogenous LKB1. Consequently, the HEK-293 experiment is a working example of a composition comprising endogenous human LKB1 (SEQ ID NO: 6), endogenous human STRADα (SEQ ID NO: 9), and endogenous human MO25α (SEQ ID NO: 11).

(B) Reply: An example of a complex comprising LKB1 of SEQ ID NO: 6, STRADα of SEQ ID NO: 9, and MO25α of SEQ ID NO: 11 does not describe the genus of all complexes comprising any protein having at least 90% identity to residues 44-343 of SEQ ID NO: 6 wherein the protein phosphorylates any polypeptide comprising a sequence with at least 90% identity to SEQ ID NO: 1-19 of SEQ ID NO: 110, plus any protein having at least 90% identity to SEQ ID NO: 9 or 10, and any protein having at least 90% identity to SEQ ID NO: 11, 13, 15, 22, or 159 such that the skilled artisan would recognize Applicants were in possession of the recited invention. See (A) Reply, above.

(C) The Rat-2 experiment is a working example of endogenous rat LKB 1 in complex with endogenous rat STRADα and endogenous rat MO25α. Enclosed Exhibit B is a BLAST comparison of SEQ ID NO: 9 with STRADα from other species, including R. norvegicus (the last comparison) showing that rat STRADα is 93% homologous to SEQ ID NO: 9; as a result the

STRADα of the Rat-2 example has at least 90% homology to SEQ ID NO: 9 as claimed. Note that rat STRADα terminates with Trp-Glu-Phe (WEF). As shown in the HomoloGene pariwise alignment score for MO25α (Exhibit C), the peptide sequence of rat MO25α is 99.4% identical to human MO25α (SEQ NO: 11). As shown in the BLAST comparison of residues 44-343 of SEQ ID NO: 6 to LKB1 from R. norwegicus (Exhibit D), rat LKB1 is 96% homologous to residues 44-343 of SEQ ID NO: 6. Therefore it can be said that the Rat-2 experiment is a working example of the composition of Claim 3.

(C) Reply: An example of a complex comprising an LKB1 having 96% identity to 44-343 of SEQ ID NO: 6, a STRADα having 93% identity with SEQ ID NO: 9, and an MO25α having 99.4% to SEQ ID NO: 11 does not describe the recited genus of encompassed complexes such that the skilled artisan would recognize Applicants were in possession of the recited invention. See (A) Reply, above.

(D) In the first part of paragraph [0166], an experiment is described in which HEK- 293 cells were transfected with mouse LKB1 fused to GST and human STRADα fused to FLAG. Complexes were then immunoprecipitated comprising transgenic mouse LKB1, transgenic human STRADα, and endogenous human MO25α (SEQ ID NO: 11). See Figure 4B, right lane.

(D) Reply: See Replies (A-C), above.

(E) In the second part of paragraph [0166] an experiment is described in which complexes were constructed of LKB1/STRADα/MO25α, LKB1/STRADα/MO25β, LKB1/STRADβ/MO25α, and LKB1/STRADβ/MO25β. All three peptides were transgenic (mouse LKB 1, human STRAD and human MO25). See Figure 4(c), in which the α isoforms of STRAD and MO25 co-purified with LKB1 in the left lane; in which STRADα and MO25β co-

purified with LKB 1 in the next-to-left lane; in which STRADβ and MO25α co-purified with LKB1 in the middle lane; and in which STRADβ and MO25β co-purified with LKB 1 in the next-to-right lane (the right lane was the negative control). The MO25α was human MO25σ (SEQ ID NO: 11), the MO25β was human MO25β (SEQ ID NO: 159), the STRADα was human STRADα (SEQ ID NO: 9), and the STRADβ was human STRADβ (SEQ ID NO: 10). Therefore, this experiment provides three additional complexes that are working examples of the claimed composition.

(E) Reply: Disclosure of complexes comprising SEQ ID NO: 9-11 and/or 159 does not describe the complexes comprising any variants thereof having at least 90% identity such that the skilled artisan would recognize Applicants were in possession of the recited invention. See (A) Reply, above.

(F) Similar compositions of the LKB 1/STRAD/MO25 complex were created in HeLa and HEK-293 cells in the experiments described in paragraphs [0167], [0169]-[0172] (five total separate experiments). These experiments used both the human MO25α and β isoforms (see paragraph [0170] for an experiment that produced a complex with MO25β) and the human STRADα and β isoforms (see paragraph [0171]). Note that the experiment in paragraph [0172] demonstrates that the complex has kinase activity in the presence of either human isoform of both STRAD and MO25.

(F) Reply: Disclosure of complexes comprising human or mouse LKB 1, STRAD, and MO25 proteins does not describe the complexes comprising any variants thereof having at least 90% identity such that the skilled artisan would recognize Applicants were in possession of the recited invention. See (A) Reply, above.

Example 2, presented in paragraphs [0243]-[0326], describes further experiments involving the claimed compositions.

(G) The experiment described in paragraphs [0246]-[0247] purified two LKB1/STRAD/MO25 complexes from rat liver extract. For both complexes (AMPKK1 and AMPKK2) endogenous rat LKB 1 was co-precipitated with endogenous rat STRADα and MO25α. As explained above, rat LKB1, STRADα and MO25α are all at least 90% homologous to the claimed SEQ ID NOs, and such complexes are thus working examples of the claimed composition.

(G) Reply: Disclosure of complexes comprising rat LKB 1, STRAD, and MO25 proteins does not describe the complexes comprising any variants thereof having at least 90% identity such that the skilled artisan would recognize Applicants were in possession of the recited invention. See (A) Reply, above.

(H) The experiments described in paragraphs [0250] and [0334] describe the construction of LKB 1/STRAD/MO25 complexes in HEK-293T cells in which transgenic LKB 1, STRAD, and MO25 were used. Complexes containing all possible combinations of STRAD and MO25 isoforms were tested for kinase activity. As shown in Fig. 15, all four complexes of wild-type LKB1 (STRADα/MO25α, STRADα/MO25β, STRADβ /MO25α, and STRADβ /MO25β) showed significant kinase activity (see lanes 6- 9). Figure 22 shows that twelve different AMPK-like proteins were activated by all four complexes. These experiments provide four additional working examples of the claimed compositions.

(H) Reply: Disclosure of complexes comprising human STRADα/MO25α, STRADα/MO25β, STRADβ /MO25α, or STRADβ /MO25β proteins does not describe the

complexes comprising any variants thereof having at least 90% identity such that the skilled artisan would recognize Applicants were in possession of the recited invention. See (A) Reply, above.

(I) The experiment described in paragraph [0253] describes the immunoprecipitation of transgenic LKB1 with endogenous MO25α and endogenous STRADα from HeLa cells. The HeLa cells normally do not express LKB1, and so active LKB1 was introduced. When HeLa cells were transformed with LKB 1, AMPK kinase activity was detected, whereas in untransformed cells there was none. This is another working example of the claimed composition in human cells, in which LKB1 is transgenic (mouse) and MO25α and STRADα are endogenous (human).

(I) Reply: See Replies (A) and (H), above.

(J) Example 2 provides two working examples of endogenous rat LKB1, MO25α and STRADα from rat liver extract; additional working examples of transgenic mouse LKB 1 with transgenic versions of all possible variations of both isoforms of human STRAD and MO25; and additional working examples of complexes of transgenic mouse LKB1 with endogenous human MO25α and endogenous human STRADα.

(J) Reply: Disclosure of complexes comprising rat, mouse, or human LKB1, MO25, and STRAD does not describe the complexes comprising any variants thereof having at least 90% identity such that the skilled artisan would recognize Applicants were in possession of the recited invention. See (A) Reply, above.

In summary, it is acknowledged that the specification and prior art provide some examples of complexes comprising rat, mouse, or human LKB1, MO25, and STRAD proteins.

However, the specification does not describe the complexes comprising variants thereof such that the skilled artisan would recognize Applicants were in possession of such variant complexes. Moreover, the specification does not describe the genus of all complexes comprising (i) any protein having at least 90% identity to residues 44-343 of SEQ ID NO: 6 wherein the protein phosphorylates any polypeptide comprising a sequence with at least 90% identity to SEQ ID NO: 1-19 of SEQ ID NO: 110, (ii) any protein having at least 90% identity to SEQ ID NO: 9 or 10, and (iii) any protein having at least 90% identity to SEQ ID NO: 11, 13, 15, 22, or 159. For example, no proteins having (i) 90-95% identity to residues 44-343 of SEQ ID NO: 6 wherein the protein phosphorylates any polypeptide comprising a sequence with at least 90-95% identity to SEQ ID NO: 1-19 of SEQ ID NO: 110, (ii) 90-95% identity to SEQ ID NO: 9 or 10, or (iii) 90-95% identity to SEQ ID NO: 11, 13, 15, 22, or 159, or complexes thereof are described. As explained abouve, the genus of all recited complexes is extremely large. Disclosure of complexes comprising rat, mouse, or human LKB1, MO25, and STRAD proteins does not described the claimed genus of complexes such that the skilled artisan would recognize Applicants were in possession of the recited invention.

Claim 3-5, 19, and 20 are herein rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. Claims 3 and 19 introduce the limitation of "an AMPK comprising a amino acid sequence having at least 90% homology to the residues 1-19 of SEQ ID NO: 110 in a T-loop binding domain". The specification fails to describe said limitation and, thus, Claims 3 and 19,

and dependent Claims 4, 5, and 20, are rejected under 35 U.S.C. 112, first paragraph, for introducing New Matter.

For these reasons and those explained in the prior action, rejection of Claims 3-5, 19, and 20 under 35 U.S.C. 112, first paragraph/written description, is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 3, as amended, is rejected under 35 U.S.C. 102(b), as being anticipated by Den Daas et al, 2000 (WO200078947). Den Daas et al teaches the human MO25 protein of SEQ ID NO: 11 herein (AAB48970; see enclosed alignment). Den Daas et al further teaches a preparation that comprises a recombinant form of said human MO25 protein isolated from human HEK 293 host cells using an antibody (pg 12, parg 3; pg 17, parg 4). Said human-derived preparation would inherently comprise (i) a human LKB1 protein having at least 90% homology to residues 44-343 of SEQ ID NO: 6 and (ii) a human STRAD protein having at least 90% homology to SEQ ID NO: 9 or 10 and comprising a C-terminal Trp-Glu-Phe tail. Therefore, Claim 3 is rejected under 35 U.S.C. 102(b), as being anticipated by Den Daas et al, 2000.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. These arguments are not found to be persuasive for the reasons following each argument.

(A) The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.

(A) Reply: It is acknowledged that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. It is required that the certain result or characteristic, more likely than not, occurs in the prior art in order to be sufficient to establish the inherency of that result or characteristic. For the reasons explained herein and in the prior action, the skilled artisan would believe that, more likely than not, the complex of Den Dass et al would comprise the human MO25 protein of SEQ ID NO: 11 herein complexed with an LKB1 protein having at least 90% homology to residues 44-343 of SEQ ID NO: 6 and a STRAD protein having at least 90% homology to SEQ ID NO: 9 or 10 and comprising a C-terminal Trp-Glu-Phe tail.

(B) At the very least, it was not inherent that using affinity chromatography with antibodies against transgenic human MO25α would produce a composition comprising the LKB 1/STRAD/MO25 complex as claimed.

The teaching in Den Daas that a polypeptide may be purified by affinity chromatography using an antibody is not limited as to the type of cell. As explained in the specification in paragraph [0161], some types of cancer cell do not express functional LKB1. For example, HeLa cells and G361 melanoma cells do not express LKB1 (see the specification at paragraphs [0009], [0162], [0244], and [0253]). As a result, depending on which type of cell was the subject of the

purification, there is no more than a mere "possibility or probability" that the result would be a complex as claimed.

(B) Reply: It is acknowledged that not all cells types endogenously express LKB1. However, Den Daas recites using HEK 293 cells, which the specification [0164] and the prior art (Boudeau et al, 2003a; cited in the specification) teach endogenously express LKB1.

(C) Den Daas provides no guidance as to what types of samples or sources can be subject to purification.

(C) Reply: Den Daas et al clearly discloses that HEK 293 cells can be used.

(D) It is possible that a given sample will contain un-complexed MO25α or MO25α incorporated in a complex other than LKB1/STRAD/MO25. As explained in paragraph [0178] of the published application, MO25 recognizes a C-terminal motif that is found not only in STRAD, but in at least 20 other known human proteins. This leaves open the possibility that MO25 forms complexes with other proteins. As a result, the purification of human MO25α could produce a composition comprising a significant quantity of complexed products other than LKB1/STRAD/MO25, and could also contain a significant quantity of un-complexed MO25.

(D) Reply: It is acknowledged that the purification of human MO25α could produce a composition comprising a significant quantity of complexed products other than LKB1/STRAD/MO25, and could also contain a significant quantity of un-complexed MO25. Nonetheless, the method specifically taught by Den Daas would also produce, more likely than not, a complex comprising human LKB1/STRAD/MO25.

For these reasons and those explained in the prior action, Claim 3, as amended, is rejected under 35 U.S.C. 102(b), as being anticipated by Den Daas et al, 2000 (WO200078947).

Rejection of Claims 3-5 under 35 U.S.C. 102(b), as being anticipated by Boudeau et al, October 2003 (IDS), as explained in the prior action, is maintained. Rejection of Claims 3-5, 19, and 20 under 35 U.S.C. 102(b) as being anticipated by Hardie et al, 2005 (US 20070036793), as explained in the prior action, is also maintained. In support of their request that said rejections be withdrawn, Applicants argue that Boudeau et al and Hardie et al are not prior art because they were published after July 17, 2003. This argument is not found to be persuasive for the following reasons. It is assumed that Applicants are arguing that Boudeau et al and Hardie et al were published after the filing date of UK 0316725. However, as explained above, the instant claims do not receive the benefit of said priority document. Therefore, Boudeau et al and Hardie et al are prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claim 19 under 35 U.S.C. 103(a) as being unpatentable over Boudeau et al, 2003 in view of Mohamed et al, 2001, as explained in the prior action, is maintained. Rejection of Claim 20 under 35 U.S.C. 103(a) as being unpatentable over the combination of Boudeau et al, 2003 and Mohamed et al, 2001 in view of Hong et al, 2003, as explained in the prior action, is also maintained. In support of their request that said rejections be withdrawn, Applicants argue that Boudeau et al and Hong et al are not prior art because they were published after July 17,

2003. This argument is not found to be persuasive because, as explained above, the instant claims do not receive the benefit of UK 0316725.

Allowable Subject Matter

No claims are allowable

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Any new references were cited solely to support rejection(s) based on amendment or rebut Applicants' arguments. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants'

remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHERIDAN SWOPE whose telephone number is 571-272-0943. The examiner can normally be reached on 11a-7:30p7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652